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INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference KP/PG5024	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/12429	International filing date *(day/month/year)* 03.11.2003	Priority date *(day/month/year)* 05.11.2002
International Patent Classification (IPC) or both national classification and IPC C07K14/005		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 14 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07.05.2004	30.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Morawetz, R Telephone No. +49 89 2399-8155

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-52 as originally filed

Claims, Numbers

1-34 as originally filed

Drawings, Sheets

1/65-65/65 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 7-9, 28, 32-34

   because:

   ☒ the said international application, or the said claims Nos. 28 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 7-9, 32-34

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

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☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-6, 10-31 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5, 13-16, 19, 20, 22, 25, 27
	No:	Claims	1-4, 6, 10-12, 17, 18, 21, 23, 24, 26, 28-31
Inventive step (IS)	Yes:	Claims	
	No:	Claims	5, 13-16, 19, 20, 22, 25, 27
Industrial applicability (IA)	Yes:	Claims	1-6, 10-27, 29-31
	No:	Claims	28: no report

2. Citations and explanations

see separate sheet

Re Item III
Non-establishment of report with regard to novelty, inventive step or industrial applicability

1. The applicant's attention is drawn to the fact that claims or part of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). Claims 7-9 and 32-34 have consequently not been examined.

2. Claim 28 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

Re Item IV
Lack of unity of invention

1. Rule 13 PCT stipulates that the international application shall relate to one invention only or to a group so linked as to form a single general inventive concept. Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding "special technical features", i.e. technical features that define a novel and inventive contribution over the prior art.

2. The only common concept (technical relationship) linking the present claims is that they are all concerned with fusion proteins comprising at least two HIV proteins or fragments or immunogenic derivatives thereof. However, this concept cannot be regarded as the "single general inventive concept" required by Rule 13.1 PCT because it is neither novel nor inventive, since such fusion proteins are already known in the art (see e.g. WO0232943; EP0577894, SALFELD J et al., EMBO Journal (1990), vol. 9, pp. 965-970; WOODBERRY T. et al., J. Virology (1999), vol. 73, pp. 5320-5325). The prior art discloses moreover polynucleotides which comprise a sequence encoding an HIV envelope protein or fragment or immunogenic derivative

thereof, fused to at least one sequence encoding an HIV non-structural or capsid protein or fragment or immunogenic derivative thereof, operably linked to a heterologous promoter (WOODBERRY T et al., J. Virology (1999), vol. 73, pp. 5320-5325; LIU WJ et al., Virology (2000), vol. 273, pp. 374-382; WO0232943). The prior art also discloses a polynucleotide encoding an HIV envelope which lacks a functional secretion signal (BOTARELLI P. et al., J. Immunology (1991), vol. 147, p. 3128-3132). The prior art moreover discloses a polynucleotide encoding codon optimized gp120 (ANDRE S., et al., J Virology (1998), vol. 72, p. 1497-1503). Polynucleotides encoding Nef, Gag, RT or Tat or fragments or immunogenic derivatives thereof are likewise well known in the prior art (see e.g. WOODBERRY T et al., J. Virology (1999), vol. 73, pp. 5320-5325; LIU WJ et al., Virology (2000), vol. 273, pp. 374-382).

3. In view of the prior art, the first problem to be solved by the present application can be defined as providing further polynucleotides which comprise a sequence encoding an HIV envelope protein or fragment or immunogenic derivative thereof, fused to at least one sequence encoding an HIV non-structural or capsid protein or fragment or immunogenic derivative thereof, operably linked to a heterologous promoter. Given that polynucleotides which comprise a sequence encoding an HIV envelope protein or fragment or immunogenic derivative thereof, fused to at least one sequence encoding an HIV non-structural or capsid protein or fragment or immunogenic derivative thereof are known in the art, seven different solutions (i.e. seven different groups of inventions) to the first problem can be identified. Namely the provision of the polynucleotide according to claim 1 or claim 2 wherein at least one non-structural or capsid protein or fragment or immunogenic derivative thereof is selected from one or more of (i) Nef, (ii) Gag, (iii) RT or (iv) Tat, the provision of (v) a polynucleotide encoding a gp120, RT, Gag and Nef-containing fusion protein, the provision of (vi) a polynucleotide encoding a gp120, Tat and Nef-containing fusion protein, and the provision of (vii) a polynucleotide encoding a gp120, Gag, Nef and Tat-containing fusion protein.

4. In view of the prior art, the second problem to be solved by the present application can be defined as providing further polynucleotides encoding a Tat containing fusion. The solution to the second problem is the provision of a polynucleotide encoding an HIV Tat molecule or fragment or immunogenic derivative in a fusion with at least two

further HIV antigens. This invention has been grouped with the 4th group of inventions.

5. In view of the fact that fusion proteins comprising at least two different HIV proteins or fragments or immunogenic derivatives thereof as well as polynulceotides which comprise a sequence encoding an HIV envelope protein or fragment or immunogenic derivative thereof, fused to at least one sequence encoding an HIV non-structural or capsid protein or fragment or immunogenic derivative thereof, operably linked to a heterologous promoter have been disclosed in the prior art, due to the essential difference in nature between the problems, due to the essential differences in structure and function of the different solutions, and due to the fact that no other technical feature can be distinguished which, in the light of the prior art, could be regarded as special technical feature, the International Examining Authority is of the opinion that there is no single inventive concept linking the present set of claims and the different inventions not belonging to a common inventive concept are the same as identified by the International Search Authority (see Form/ISA/210).

Re Item V

Reasoned statement under Article 35(2) PCT with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Invention 1: claim 6 (completely) and claims 1-3, 10-21, 23-31 (all partially)

1. Reference is made to the following documents, the numbering corresponds to the listing of the documents in the international search report:

D1: WOODBERRY T ET AL., JOURNAL OF VIROLOGY, THE AMERICAN SOCIETY FOR MICROBIOLOGY, US, vol. 73, no. 7, July 1999 (1999-07), pages 5320-5325

D2: LIU W J ET AL., VIROLOGY, ACADEMIC PRESS,ORLANDO, US, vol. 273, no. 2, 1 August 2000 (2000-08-01), pages 374-382

D3: WO 01/27291 A

D4: WO 02/32943 A

D5: EP-A-0 577 894

D6: BENKO D M ET AL., JOURNAL OF VIROLOGY, vol. 64, no. 6, 1990, pages

2505-2518

D7: SALFELD J ET AL., EMBO JOURNAL, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 9, no. 3, 1 March 1990 (1990-03-01), pages 965-970

D8: WO 98/41536 A

D9: DOE B ET AL., EUROPEAN JOURNAL OF IMMUNOLOGY, WEINHEIM, DE, vol. 24, no. 10, 1994, pages 2369-2376

D10: BOTARELLI P ET AL., JOURNAL OF IMMUNOLOGY, THE WILLIAMS AND WILKINS CO. BALTIMORE, US, vol. 147, no. 9, 1 November 1991 (1991-11-01), pages 3128-3132

D11: STEFANIE A ET AL., JOURNAL OF VIROLOGY, THE AMERICAN SOCIETY FOR MICROBIOLOGY, US, vol. 72, no. 2, February 1998 (1998-02), pages 1497-1503

D12: KOTSOPOULOU E ET AL., JOURNAL OF VIROLOGY, THE AMERICAN SOCIETY FOR MICROBIOLOGY, US, vol. 74, no. 10, May 2000 (2000-05), pages 4839-4852

D13: WO 02/36792 A

2. Subject-matter of the application

Present application relates to a polynucleotide which comprises a sequence encoding an HIV envelope protein fused to at least one sequence encoding an HIV non-structural or capsid protein (nef, tat, RT or gag of HIV), operably linked to a heterologous promoter.

3. The present application does not satisfy the criterion set forth in **Article 33(2) PCT** because the subject-matter of claims 1-3, 6, 10-12, 17, 18, 21, 23, 24, 26, 28-31 is not new in respect of prior art as defined in the regulations **(Rule 64(1)-(3) PCT)**.

3.1. D1 discloses a **Nef-Pol-Gag-Nef-Pol-gp120-Nef** polytope fusion protein coding for seven HIV HLA A2 CTL epitopes conjoined in a single artificial construct (abstract, Fig.1, Table 1). The full-length gel-purified fragment was cloned into the EcoRV site of pBluescript II KS(-) and checked by sequencing. The insert was then subcloned behind the vaccinia virus p7.5 promoter in the plasmid shuttle vector pPS 7.5 A with BamHI and SalI (page 5321, left hand column, first paragraph). HHD mice vaccinated with the HIV polytope were shown to generate CTL specific for multiple epitopes. The

use as a prophylactic polytope vaccine is likewise disclosed (page 5324, left hand column, last paragraph). Since the fusion protein contains no secretion signal it is neither glycosylated nor secreted from the cell.

D1 thus anticipates the subject-matter of claims 1-3, 6, 10-12, 17, 18, 21, 23, 24, 26, 28-31.

3.2. D2 discloses papilloma virus virus-like particles for the delivery of multiple cytotoxic T cell epitopes. The artificial "polytope" minigene contains known CTL epitopes of HIV IIIB gp120, nef, and RT (Figure 1, Table 1). The polytope fusion protein was produced in Sf-9 insect cells infected with recombinant baculovirus, purified and used to immunize various mice. The in vivo induction of antibody and CTL response by the polytope fusion protein was shown (Figure 4 and Figure 6). Since the fusion protein contains no secretion signal it is neither glycosylated nor secreted from the cell.

D2 thus anticipates the subject-matter of claims 1-3, 6, 11, 12, 17, 18, 21, 23, 24, 26, 28-31.

3.3. D3 discloses a polyepitopic gag, pol, env, nef containing construct for the induction of HLA-A2.1 restricted HIV-1 specific CTL response in HHD mice (example 11, Fig. 5, Table 5) and likewise anticipates the subject-matter of claims 1-3, 6, 10-12, 17, 18, 21, 23, 24, 26, 28-31.

3.4. D4 discloses (page 43, line 4 - page 47, line 21; Table 1) various DNA constructs encoding **env-nef** fusion proteins in which the env protein has been codon optimized for expression in human cells. D4 also discloses mutants in which conserved N-linked glycosylation sites were eliminated by site-directed mutagenesis. Pharmaceutical compositions, methods of treatment and prime boost vaccination strategies are likewise disclosed (page 162, claims). D4 thus anticipates the subject-matter of claims 1, 3, 17, 18, 21, 23, 24, 26, 28-31.

3.5. D5 discloses a gag-env fusion protein encoding DNA construct (Fig. 3), chimeric proteins and vaccines comprising the chimeric proteins (abstract). Since the fusion protein contains no secretion signal it is neither glycosylated nor secreted from the cell. D5 thus anticipates the subject-matter of claims 1-3, 11, 12, 17, 18, 21, 23, 24,

28-31.

3.6. D6 and D7 which both disclose fusionproteins comprising coding sequences of **tat, env and rev** are considered to anticipate the subject-matter of claims 1-3, 6, 11, 12, 17, 18, 21.

3.7. The subject-matter of claims 13-16, 19, 20, 25, 27 appears to be new in view of the available prior art.

4. The present application does not satisfy the criterion set forth in **Article 33(3) PCT** because the subject-matter of claim 13-16, 19, 20, 25, 27 does not involve an inventive step as defined in the regulations **(Rule 65 (1)-(2) PCT)**.

4.1. Claim 13 which relates to the polynucleotide according to any one of claims 1 to 12 wherein one or more of the sequences encoding gp120, Nef, Gag, RT or Tat is or are codon optimised to resemble the codon usage in a highly expressed human gene is considered to lack an inventive step in view of the disclosure of any of D1 - D7 in combination with the teaching of D11 or D12.

D11 discloses that optimized codon usage of the gp120 sequence considerably increased both humoral and cellular immune response during DNA vaccination. D12 discloses that codon optimization of HIV-1 gag-pol gene results in a 10-fold increase in steady-state levels of cognate RNA with an equivalent 10-fold increase in protein production.

4.2. Claim 14, which relates to various polynucleotide sequences which all comprise a codon optimised gp120 is likewise considered to lack an inventive step in view of the disclosure of any of D1 -D7 in combination with the teaching of D11 or D12.

4.3. Claims 15 and 16 which relate to the polynucleotide according to any one of claims 1 to 14 wherein the promoter is the promoter from HCMV IE gene are considered to lack an inventive step in view of the disclosure of any of D1 -D7 in combination with the teaching of D13 which discloses this promoter and its use for the expression of HIV-1 antigens (page 5, line 32 - page 7, line 4).

4.4; Claims 19 and 20 which relate to the use of a replication defective adenovirus vector are considered to lack an inventive step in view of D4 which discloses the use of adenoviruses (page 25, lines 16-35) for the expression of the env-nef encoding fusion proteins.

4.5. Claim 25 which relates to a pharmaceutical composition according to claim 24 wherein the carrier is a plurality of particles such as gold particles is considered to lack an inventive step in view of the disclosure of any of D1 -D7 in combination with the teaching of D13 which discloses (example 2) the preparation of plasmid-coated "gold slurry" for vaccination purposes.

4.6. Claim 27 which relates to an intradermal delivery device comprising a pharmaceutical composition according to any one of claims 24 to 26 is likewise considered to lack an inventive step in view of the disclosure of any of D1 -D7 in combination with the teaching of D13 which discloses (page 16, line 14 - page 17, line 14) various devices for the intradermal delivery of the plasmid DNA.

Regarding claim 11 applicant's attention is also drawn to D9 which discloses that the induction of CTL responses was considerably less efficient when mice were immunized with gp120CHO, a native, fully glycosylated envelope protein produced in mammalian CHO cells. Denaturation of gp120CHO prior to immunization was not sufficient to prime CTL responses. However, envelope-specific CD8+ CTL activity was elicited when N-linked glycans were removed by treatment with an endoglycosidase.

Regarding claim 12 applicant's attention is also drawn to D10 which relates to N-glycosylation of HIV gp120 and discloses that the lack of signal sequence prevents passage through the secretory pathway and addition of carbohydrates (page 3128, right hand column, first full paragraph).

Invention 2: claims 4, 5, 22 (all completely) and claims 1-3, 10-21, 23-31 (all partially)

1. Reference is made to the following documents, the numbering corresponds to the listing of the documents in the international search report:

D1: WOODBERRY T ET AL., JOURNAL OF VIROLOGY, THE AMERICAN SOCIETY FOR MICROBIOLOGY, US, vol. 73, no. 7, July 1999 (1999-07), pages 5320-5325

D3: WO 01/27291 A

D11: STEFANIE A ET AL., JOURNAL OF VIROLOGY, THE AMERICAN SOCIETY FOR MICROBIOLOGY, US, vol. 72, no. 2, February 1998 (1998-02), pages 1497-1503

D12: KOTSOPOULOU E ET AL., JOURNAL OF VIROLOGY, THE AMERICAN SOCIETY FOR MICROBIOLOGY, US, vol. 74, no. 10, May 2000 (2000-05), pages 4839-4852

D13: WO 02/36792 A

D14: IGLESIAS, ENRIQUE ET AL., JOURNAL OF BIOCHEMISTRY, MOLECULAR BIOLOGY AND BIOPHYSICS , vol. 5(2), pages 109-122, 2001

D15: CA-A-2 430 702

2. Subject-matter of the application

Present application relates to a polynucleotide which comprises a sequence encoding an HIV envelope protein fused to at least one sequence encoding an HIV non-structural or capsid protein operably linked to a heterologous promoter, wherein the polynucleotide encodes a gp120, RT, Gag, and Nef- containing quadrivalent fusion protein.

3. The present application does not satisfy the criterion set forth in **Article 33(2) PCT** because the subject-matter of claims 1-4, 10-12, 17, 18, 21, 23, 24, 28-31 is not new in respect of prior art as defined in the regulations (**Rule 64(1)-(3) PCT**).

3.1. The polynucleotide encoding the Nef-Pol-Gag-Nef-Pol-gp120-Nef polytope fusion protein disclosed in D1 (Fig. 1) is considered to fall within the scope of claims 1- 4. D1 thus anticipates the subject-matter of claims 1-4, 10-12, 17, 18, 21, 23, 24, 26, 28-31.

3.2. The polyepitopic gag, pol, env, nef containing construct disclosed in D3 (example 11) is considered to fall within the scope of claims 1-4. D3 thus also anticipates the subject-matter of claims 1-4, 10-12, 17, 18, 21, 23, 24, 26, 28-31.

3.3. D14 discloses a chimeric gene, termed C3, which comprises fragments from the HIV-1 gp120, gp41, RT, vpr, p24 and nef genes (page 110, right hand column, first full paragraph; Fig. 1). Recombinant protein C3 was produced in E. coli, purified (page 112, right hand column, second full paragraph) and used to immunize female Balb/c mice (page 115, right hand column, last paragraph). According to D14 the chimeric gene is ready to be used in vaccine strategies at eliciting cell-mediated immune responses, such as vaccines based on naked DNA, viral vectors, or bacterial vectors. Since the fusion protein contains no secretion signal it is neither glycosylated nor secreted from the cell. D14 thus anticipates the subject-matter of claims 1-4, 10-12, 17, 18, 21, 23, 24, 28-31.

3.4. D15 also discloses the chimeric C3 gene which contains epitopes from the HIV-1 gp120, RT, Gag and nef genes (page 8, lines 6-19; example 1-11). The fusion protein, vectors and pharmaceutical compositions are likewise disclosed. D15 thus anticipates the subject-matter of claims 1-4, 10-12, 17, 18, 21, 23, 24, 28-31.

3.5. The subject-matter of claims 5, 13-16, 19, 20, 22, 25-27 appears to be novel in view of the available prior art.

4. The present application does not satisfy the criterion set forth in **Article 33(3) PCT** because the subject-matter of claims 5, 13-16, 19, 20, 22, 25-27 does not involve an inventive step as defined in the regulations (**Rule 65 (1)-(2) PCT**).

4.1. Claim 5 relates to a polynucleotide according to claim 4 wherein the fusion is selected from gp120-RT-Nef-Gag and RT-Nef-Gag-gp120.

D14 discloses a polynucleotide which encodes a gp120-gp41-vpr-RT-Nef-Gag fusion protein (abstract, Fig. 1). This protein was designed for vaccine strategies directed at raising cellular immune responses to HIV-1 and comprises epitopes which elicit mainly CTL responses. The provision of a variant comprising sequences corresponding to 4 of the 6 proteins disclosed in D14 or D15 is considered an arbitrary selection devoid of any inventive activity.

Claim 5 is also considered to lack an inventive step in view of D2 which discloses a polynucleotide encoding a gp120-nef-RT containing fusion protein in combination

with e.g. D5, which discloses a gag-env fusion protein encoding DNA construct.

4.2. Claims 13 and 14 are considered to lack an inventive step in view of the teaching of D14 or D15 in combination with the teaching of D11 or D12.

4.3. Claims 15, 16, 25-27 are considered to lack an inventive step in view of the teaching of D14 or D15 in combination with the teaching of D13.

4.4. Claims 19 and 20 are considered to lack an inventive step in view of D15 which also discloses the use of adenoviruses (page 10, lines 4-8).